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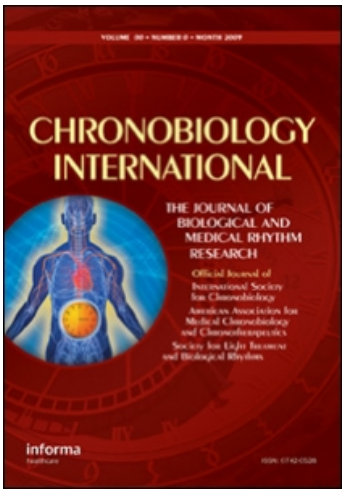

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NO IMPACT OF PHYSICAL ACTIVITY ON THE PERIOD OF THE CIRCADIAN PACEMAKER IN HUMANS

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ABSTRACT

The intrinsic period τ of the circadian pacemaker in humans was investigated by means of forced desynchrony. In this protocol, during 6 scheduled days, the sleep-wake alternation was forced to a period of 20h (i.e., 13.5h for wakefulness and 6.5h for sleep). Light intensity was kept below 10 lux. Three experiments were performed. In experiment 1, 12 subjects were free to spend the available time studying, watching videos, and reading books. In experiment 2, at 2h intervals, 11 subjects spent 6 half-hour sessions per subjective day cycling with minimal effort on a cycle trainer, resulting in an average increase of heart frequency of less than 10 beats per minute. In experiment 3, 11 subjects spent the same intervals of time cycling, but now during 20 minutes per session at an average heart rate of between 140 and 150 beats per minute. Core body temperature was measured continuously. A deconvolution technique discriminated the impact of the circadian pacemaker on body temperature from the impact of activities related to sleeping and waking. From this analysis, the period of the pacemaker was derived. We found the following results: experiment 1, $\tau = 24.30 \pm 0.36$h; experiment 2, $\tau = 24.17 \pm 0.45$h; experiment 3, $\tau = 23.98 \pm 0.42$h. The trend of shorter τ at higher levels of physical activity was not statistically significant. We conclude that τ in humans, determined under conditions of forced desynchrony, is very close to 24h. The suggestion from the literature that single activity pulses would predominantly yield phase delays of the circadian pacemaker is not confirmed by these multiple pulse experiments because no lengthening of τ with increasing effort was observed. (*Chronobiology International, 15(1), 49–57, 1998*)

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INTRODUCTION

Since the discovery of circadian rhythmicity in humans persisting under conditions of temporal isolation (1), the impact of environmental conditions on τ (i.e., the period of the free-running activity rhythm) has received considerable attention. On average, τ has been estimated as about 24.9h (2). Changes of τ were observed in response to changes in environmental light intensity, "social zeitgeber strength," and the strength of environmental electromagnetic fields (2). Manipulations of workload, in contrast, did not lead to systematic changes in τ (3,4). The presence of naps in the course of temporal isolation did seem to shorten τ to values close to 24h (5).

Since then, much attention has been paid to the impact of light pulses on the human circadian system (6–11). It is known now that light is the main zeitgeber in humans, and other influences are of relatively minor importance in resetting the circadian pacemaker. As was already experimentally observed in early studies (12), it was recently demonstrated on the basis of simulations that the light levels in the old bunker studies were sufficient to modify the period of overt rhythms detectably (13). The bunker studies did not, therefore, yield systematic information on the intrinsic period of the pacemaker, but on the pacemaker in interaction with a self-selected light-dark cycle.

It has thus become clear that, for better estimates of τ, experiments should be performed in near total darkness and under conditions of forced desynchrony. In this protocol, the intervals for sleep are systematically shifted through all circadian phases by applying T cycles (i.e., sleep plus wake durations) that deviate substantially from the intrinsic period of the pacemaker, which is around 24h. Any possible zeitgeber effect on the circadian pacemaker would then become of limited influence on the results because advances and delays would both occur in the course of the experiment. Indeed, the values of τ obtained under conditions of forced desynchrony are smaller than 24.9h. Often, they are approximately 24.1h to 24.3h (14, 15).

It remains possible that phase-shifting influences induced by the behavioral sleep-wake cycle are still present in forced desynchrony studies, which then would still yield τ values that deviate from the intrinsic τ. This can be tested by varying the strength of those hypothetical zeitgebers. One possible variable with zeitgeber properties could be motor activity (16). In animals, it has been demonstrated that pulses of motor activity may lead to phase shifts of the circadian pacemaker (17,18) and that access to a running wheel shortens τ (19,20). More generally, it seems that τ covaries with the amount of activity, such as under the influence of gonadal hormones (21) and age (22). In humans, pulses of activity have resulted in immediate changes in the circadian pattern of physiological variables, which are consistent with—but not necessarily caused by—phase shifts of the circadian pacemaker. In two studies, activity pulses were applied during the night. They seemed only to induce phase delays (23,24). No clear phase advances were observed in the acute responses of several physiological parameters. In two other studies, activity pulses were applied during spontaneous wakefulness in experiments under temporal isolation. These pulses did not lead to systematic changes in the free-running period (3,4). Taken together, these studies suggest that activity pulses in humans induce only

phase delays. If activity in humans would induce only phase delays, this would imply that τ (as determined in forced desynchrony experiments) would lengthen with an increase of motor activity. It could then be that the observed values of approximately 24.2h correspond to a certain level of activity, and that lower values would be obtained at low levels of activity.

This is the central question of the present investigation: Does circadian τ lengthen with increasing physical activity?

SUBJECTS AND METHODS

In this study, the values of τ were estimated from the results of core body temperature registrations obtained in a forced desynchrony protocol. After a period of four days of restricted activity and scheduled bedtimes at home and after an adaptation period of one evening and one night in the isolation unit, the forced desynchrony protocol lasted for 120h. A T cycle of 20h was applied, which resulted in 6 subjective days of 13.5h and nights of 6.5h during the 5 days of each recording. All six subjective days were identical with respect to the timing of showering, meals, psychological ratings, performance tests, and the intervals for physical activity. During forced desynchrony, light intensity was kept below 10 lux in order to minimize the influence on the circadian pacemaker of light-dark transitions at lights off and lights on.

Physical activity was varied over three experiments. Experiment 1 was performed with a very low level of physical activity: Subjects were allowed to watch videos, read books, or prepare for an examination. The subjects were 12 healthy males with ages between 21 and 25 years (mean 23.7 ± 1.4 years). Experiment 2 was performed at an intermediate level of physical activity: Subjects cycled on a cycle trainer for half an hour per 2h of each subjective day at a rate that did not lead to an average increase of heart rate beyond 10 beats per minute. The subjects were 11 healthy males with ages between 21 and 24 years (mean 22.8 ± 1.0 years). Experiment 3 was performed at a high level of physical activity: Subjects cycled on a cycle trainer for half an hour every 2h in each wake time. During 20 minutes of each session, this led to an average heart rate between 140 and 150 beats per minute. The subjects were 11 healthy males with ages between 20 and 25 years (mean 21.9 ± 1.3 years). No subject participated in more than one experiment. The experiments were performed between February 1994 and December 1995.

The τ was determined by means of a deconvolution technique. This was done as follows (15). First, the core body temperature signal (Fig. 1A) was folded at the imposed period of 20h to obtain the average course of body temperature over the subjective day and night. The resulting curve covers 20h and is plotted 6 times in Fig 1B. Due to the fact that sleep and wakefulness were shifted through all phases of the circadian pacemaker, little pacemaker influence remained in the signal after the folding. The curve of Fig. 1B almost exclusively represents the "masking" influences on core body temperature. Subsequently, subtracting this masking effect from the raw data (Fig. 1C) yielded a curve that varies approximately sinusoidally and has a period of nearly 24h. The period of this signal was determined by autocorrelation. In principle, the obtained period is the desired result. However, due to the fact that not all circadian phases are exactly equally represented in the first step of the analysis (i.e., the folding at the imposed period), an even better estimate of τ can be obtained by iteration. From Fig. 1C, the best estimate of the circadian pacemaker contribution can be obtained by folding the curve at the

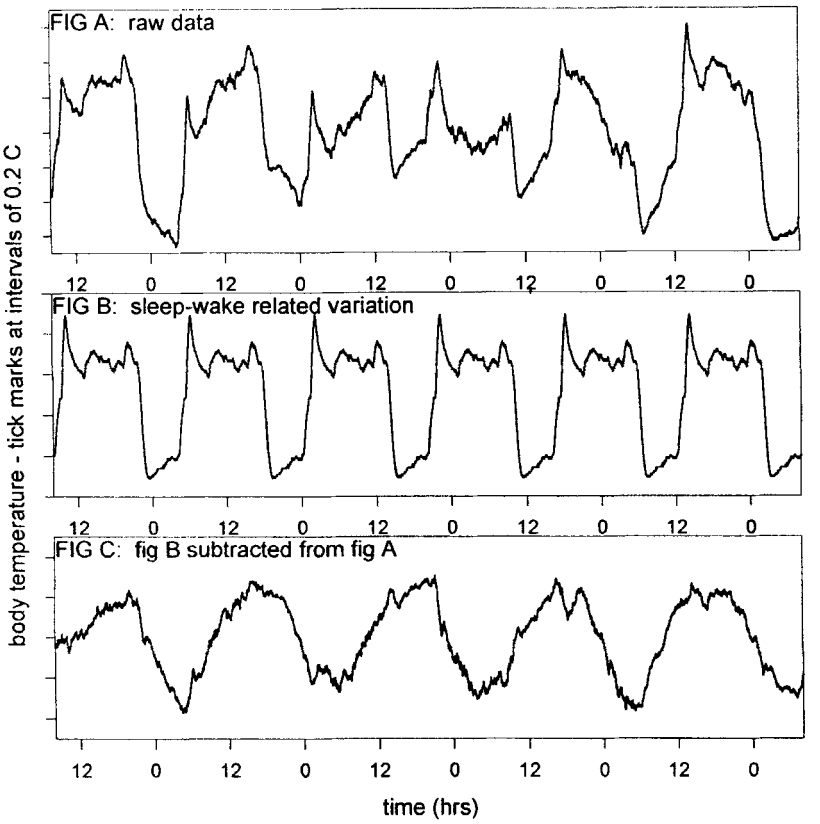

FIGURE 1. Example of the deconvolution procedure to obtain the impact of the circadian pacemaker on core body temperature. Top panel: Example of the course of core body temperature during forced desynchrony. Middle panel: Result of folding the top panel data at a 20h period, plotted 6 times. Bottom panel: The result of subtracting the middle panel data from the top panel data.

period of τ. Subtracting the resulting curve from the raw data yielded a curve that predominantly consists of the masking influences. From this curve, the entire procedure was repeated until, in a few steps, a stable solution for τ was obtained.

This method was applied to experiments 1 and 2. In experiment 3, however, the raw data show very pronounced peaks in body temperature at the instances of high physical activity (Fig. 2). It can be expected that small differences in peak size and peak timing from (scheduled) day to day can restrict the possible values for τ that result from the analysis to certain narrow intervals. This is due to rudimentary cycling peaks in the signal after subtraction of the masking component. Whenever these rudimentary peaks are superimposed in the autocorrelation procedure, a (local) maximum in the amount of explained variance will be observed. Obviously, this can lead to misestimation of τ. Such misestimation can be prevented by a procedure in which the individual peaks due to the cycling are first filtered out. This was done as follows. For each subject of experiment 3, the average shape of the peaks due to cycling was calculated. Then, for each individual

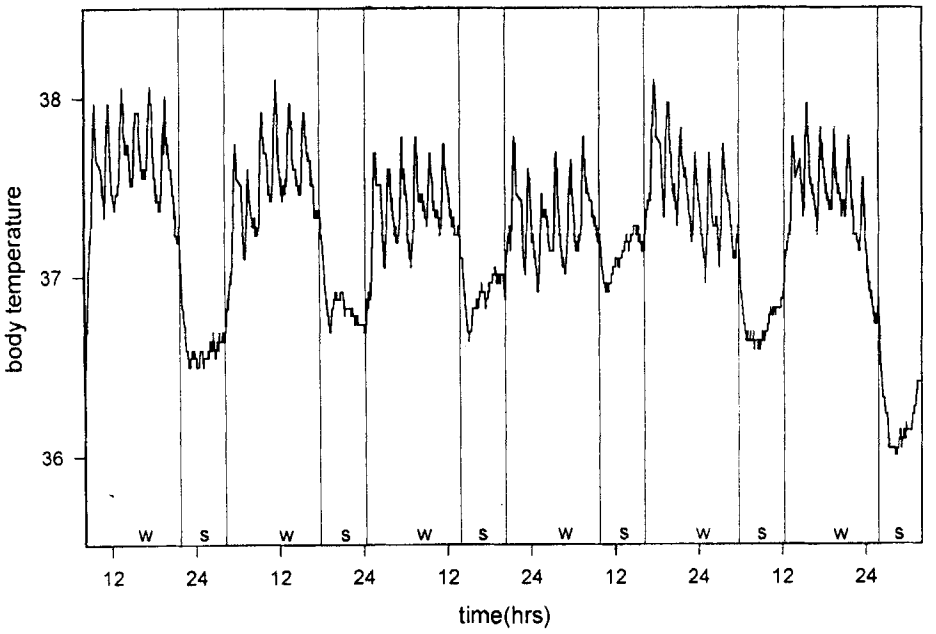

FIGURE 2. Example of the core body temperature registration of a single subject who cycled on a cycle trainer six times per subjective day. This was done at 2h intervals, at 70% VO_2-max.

peak, the amplitude and phase required to fit the average peak best to the data was determined. Finally, the adjusted average peak was subtracted from the raw data, and the resulting curves were analyzed in the way described above, as if no cycling had occurred.

Taking showers, defecation, and technical problems resulted in gaps in the recordings. In total, data were missing for about 10% of the total recording time. Intervals of missing data that were shorter than 1.5h were filled by linear interpolation.

RESULTS

The three experiments yielded the following average values of τ (Table 1).

Experiment 1 (no physical activity): $\tau_1 = 24.30$, SD 0.36h
Experiment 2 (intermediate activity): $\tau_2 = 24.17$, SD 0.45h
Experiment 3 (high activity): $\tau_3 = 23.98$, SD 0.42h

The results of experiment 3 were obtained after filtering of the peaks in the temperature curves induced by cycling (see Methods section). Without filtering, the results of experiment 3 are $\tau = 24.09$, SD 0.41h.

While the results of experiment 1 are significantly different from 24h (sign test, $p = 0.016$), this does not hold for experiments 2 and 3. An analysis of variance does not reveal a significant relationship between τ and physical activity level, with $F(33,2) = 1.59$ and $p = .22$. The number of subjects showing a τ value below 24h was 2/12 for experiment 1, 3/11 for experiment 2, and 7/11 for experiment 3.

Table 1. τ in Decimal Hours

Experiment 1 (no exercise)	Experiment 2 (low effort)	Experiment 3 (high effort)
23.63	24.25	23.43
24.38	24.23	23.83
24.78	23.38	23.88
24.52	23.48	23.75
24.25	24.00	24.40
24.45	24.22	23.95
24.18	23.92	24.45
24.00	24.18	24.70
23.65	24.40	24.22
24.67	24.76	23.28
24.42	24.98	23.93
24.72		
Mean ± SD = 24.30 ± 0.36	Mean ± SD = 24.17 ± 0.45	Mean ± SD = 23.98 ± 0.42

Note: No subject participated in more than one experiment.

DISCUSSION

This is the first study to explore systematically the impact of physical activity on the intrinsic period of the human circadian pacemaker under strictly controlled conditions. No consistent influences could be detected. This could be due to one of two possible causes: (i) the method is not sensitive enough, or (ii) the effects are very small.

Although the method of analysis is straightforward in the way it yields values of τ, it has limitations. A major limitation of the method is that it is based on just one single beat period of imposed period and intrinsic period: After 6 scheduled days, the imposed schedule of a period of 20h for the first time occurs at a similar circadian phase as at the start of the study. The entire beat period is used for the determination of τ. As a consequence, the method is sensitive to fluctuations in core body temperature that do not directly result from the protocol, including possible transients near the beginning of the protocol. As long as these fluctuations are not systematic, but occur at random moments during the protocol, the influence on τ will be unsystematic as well and merely increase the standard deviation of the results. Under the assumption that the adaptation period included in the design was sufficiently long for the subjects to adapt to the circumstances, it seems justified to assume that those fluctuations are unsystematic. Hence, we think that the average values of τ obtained in this study do represent the average intrinsic values of the circadian pacemakers of the subjects. The fact that the values of τ obtained in experiment 1 (24.30 ± 0.36h) are very similar to those obtained in studies of four beat periods in experiments by Czeisler et al. (14) suggests that transients at the beginning of the experiments can be neglected.

Another limitation of the method is that it is based on the assumption that the various contributions to core body temperature are additive. As was demonstrated elsewhere (15), the body temperature data of these experiments strongly support this assumption.

Sleep efficiency has been reported to vary with circadian phase in the course of forced desynchrony studies (25). This may have an impact on body temperature. In the

present study, sleep efficiency data have not yet been analyzed. However, since the fraction of time available for sleep is smaller in the present study (32.5%) compared to the literature (33.3%), it is to be expected that the small effects of sleep efficiency on body temperature are even smaller in the present study.

Few data are available on the effect of increased physical activity on characteristics of the circadian pacemaker in humans (16). Single activity pulses by cycling on a cycle trainer for 3 hours and applied during the night seemed to induce phase delays of the pacemaker as determined by monitoring various physiological rhythms (23). Similarly, hourly 15-minute cycling sessions repeated for 8h during the night shift induced a small, but significant, delay of the phase of the circadian pacemaker (24). Phase advances did not seem to occur. However, those studies did not include activity pulses during habitual wake time. Activity pulses during wakefulness were applied in two early studies of the circadian system under conditions of temporal isolation (3,4). Those studies did not reveal systematic changes of τ in response to activity pulses applied during the subjective day. Generalizing these findings to the present study, one would expect that phase delays would accumulate during the protocol in response to the pulses of increased physical activity applied during habitual sleep time. As a consequence, one would expect τ to lengthen with increasing intensity of physical activity. This expectation is not met by the data. In contrast, a nonsignificant trend toward a shortening of τ as a function of increasing intensity of activity is observed. If some activity pulses in the protocol of repeated activity would have induced phase delays of the circadian pacemaker, this means that other pulses must have induced phase advances. Alternatively, the impact of each pulse on the pacemaker in the present protocol could have been so small that it remained undetected.

A substantial fraction of the study population (35%) yielded τ values shorter than 24h. Given the relative imprecision of the method, this could be due to the method itself, while the actual intrinsic periods are all over 24 h. Yet, it seems conceivable that the intrinsic value of τ is very close to 24h (5,14). If this would be the case, in normal daily life no daily adjustments of circadian phase would be required, and the circadian pacemaker would be much more stable than previously assumed. By being so stable, the pacemaker signal would be much more suited to detect, for instance, seasonal changes in night length than could be expected previously. With τ close to 24h, the pacemaker meets the requirements needed to function as "a clock for all seasons" (26).

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REFERENCES

1. Aschoff J, Wever, RA. Spontanperiodik des Menschen bei Ausschluss aller Zeitgeber. *Naturwissenschaften* 1962; 49:337–42.
2. Wever RA. *The human circadian system.* Berlin: Springer, 1979.

3. Webb WB, Agnew HW Jr. Sleep and waking in a time-free environment. *Aerospace Med* 1974; 45:617–22.
4. Wever RA. Influence of physical workload on freerunning circadian rhythms of man. *Pflügers Arch* 1979; 381:119–26.
5. Campbell SS, Dawson D, Zulley J. When the human circadian system is caught napping: evidence for endogenous rhythms close to 24 hours. *Sleep* 1993; 16: 638–40.
6. Czeisler CA, Richardson GS, Zimmerman JC, Moore-Ede MC, Weitzman ED. Entrainment of human circadian rhythms by light-dark cycles: a reassessment. *Photochem Photobiol* 1981; 34:239–47.
7. Dijk DJ, Visscher CA, Bloem GM, Beersma DGM, Daan S. Reduction of human sleep duration after bright light exposure in the morning. *Neurosci Lett* 1987; 73: 181–86.
8. Dijk DJ, Beersma DGM, Daan S, Lewy AL. Bright morning light advances the human circadian system without affecting NREM homeostasis. *Am J Physiol* 1989; 256:R106–R111.
9. Honma K, Honma S. A human phase response curve for bright light pulses. *Japan J Psychiat Neurol* 1988; 42:167–68.
10. Jewett ME, Kronauer RE, Czeisler CA. Light-induced suppression of endogenous circadian amplitude in humans. *Nature* 1991; 350:59–62.
11. Minors DS, Waterhouse JM, Wirz-Justice A. A human phase-response curve to light. *Neurosci Lett* 1991; 133:36–40.
12. Wever R. Der Einfluß des Lichtes auf die circadiane Periodik des Menschen. I. Einfluß auf die autonome Periodik. *Z Physik Med* 1973; 3:121–34.
13. Klerman EB, Dijk DJ, Kronauer RE, Czeisler CA. Simulations of light effects on the human circadian pacemaker: implications for assessment of intrinsic period. *Am J Physiol* 1996; 270:R271–R282.
14. Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Dijk DJ, Rimmer DW, Ronda JM, Allan JS, Emens JS, Kronauer RE. Reassessment of the intrinsic period (τ) of the human circadian pacemaker in young and older subjects. *Sleep Res* 1995; 24A:505.
15. Hiddinga AE, Beersma DGM, Van den Hoofdakker RH. Endogenous and exogenous components in the circadian variation of core body temperature in humans. *J Sleep Res* 1997; in press.
16. Redlin U, Mrosovsky N. Exercise and human circadian rhythms: what we know and what we need to know. *Chronobiol Internat* 1997; 14:221–29.
17. Reebs SG, Lavery RJ, Mrosovsky N. Running activity mediates the phase-advancing effects of dark pulses on hamster circadian rhythms. *J Comp Physiol A* 1989; 165:811–18.
18. Reebs SG, Mrosovsky N. Large phase-shifts of circadian rhythms caused by induced running in a re-entrainment paradigm: the role of pulse duration and light. *J Comp Physiol A* 1989; 165:819–25.
19. Yamada N, Shimoda K, Ohi K, Takahashi S, Takahashi K. Free-access to a running wheel shortens the period of free-running rhythms in blinded rats. *Physiol Behav* 1988; 42:87–91.
20. Edgar DM, Kilduff TS, Martin CE, Dement WC. Influence of running wheel activity on free-running sleep/wake and drinking circadian rhythms in mice. *Physiol Behav* 1991; 50:373–78.

21. Daan S, Damassa D, Pittendrigh CS, Smith ER. An effect of castration and testosterone replacement on a circadian pacemaker in mice (*Mus musculus*). *Proc Nat Acad Sci USA* 1975; 72:3744–47.
22. Weinert D, Weiß T. A nonlinear interrelationship between period length and the amount of activity. Age-dependent changes. *Biol Rhythm Res* 1997; 28:105–20.
23. Van Reeth O, Sturis J, Byrne MM, Blackman JD, L'Hermite-Balériaux M, Leproult R, Oliner C, Refetoff S, Turek FW, Van Cauter E. Nocturnal exercise phase delays circadian rhythms of melatonin and thyrotropin secretion in normal men. *Am J Physiol* 1994; 266:E964–E974.
24. Eastman CI, Hoese EK, Youngstedt SD, Liu L. Phase-shifting circadian rhythms with exercise during the night shift. *Physiol Behav* 1995; 58:1287–91.
25. Dijk DJ, Czeisler CA. Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. *Neurosci Lett* 1994; 166:63–68.
26. Pittendrigh CS, Daan S. A functional analysis of circadian pacemakers in nocturnal rodents. V. Pacemaker structure: a clock for all seasons. *J Comp Physiol* 1976; 106: 333–55.